III. REMARKS

Claim Status

Claims 1-7, 9 and 11-14 are active in the application. Claim 7 has been canceled. Claims 1 9 and 11 have been amended.

Claim Objections

Claims 1, 7, and 9 are objected to because of the following informalities: improper grammar in the lists of primers as there is no punctuation as with a comma separating each of the SEQ ID NOs.

Applicant has added commas and otherwise corrected the grammar thus obviating the ground for objection.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 1-7, 9, and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in that:

1. Claims 1, 7, and 9 recite lists of primers in the alternative, that is recite "or alternatively". As independent claims 1, 7, and 9 are unclear, dependent claims 1-7, 9, and 11-13 are also unclear.

Applicant has deleted the offending phrase thus obviating this ground for rejection.

2. Claims 1-6 and 12-14 are rejected as being incomplete for omitting essential steps, such omission amounting to a

gap between the steps.

The omitted steps are: how the cancer is detected as recited in the preamble of claim 1. Although "performing mutational analysis" is recited in the last line of claim 1, it is unclear what results(s) of mutational analysis would qualify as non-invasive early detection of colon cancer or intestinal cancer precursor cells.

The examiner states that neither the claims nor the specification provide a definition of the mutational analysis needed for the recited detection of colon cancer or intestinal cancer precursor cells.

Applicant respectfully traverses the rejection and points the examiner's attention to page 14, third full paragraph of applicant's specification where the any analysis is stated to be for the detection of mutations in specific genes. The procedures employed in a mutational analysis are commonly known and it is only the mutations themselves which need to be specified. It is stated throughout the specification and claims where the genes to be analyzed for mutations are APC, K-ras, β-catenin and B-raf.

Applicant has amended the claims to indicate that it is a mutation in the 4 listed genes that is the test for the detection of cancer thus obviating this ground for rejection.

3. Claims 7 and 9 recite an improper Markush group because of the use of the term "comprising".

Applicant has amended the claims to change the terminology to "consisting of" thus obviating this ground for rejection.

4. Claim 11 provides for a method of using the kit of claim 9, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass.

Claim 11 has been amended to recite that it is used in the method of claim 1 thus obviating this ground for rejection.

Claim Rejections - 35 USC § 103

Claims 7, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kmiec et al. or over Shuber et al. (W0200173002 published 2001) or over Ferrie et al. (GB2327497 published 1999) or over Coste et al. (1998), Nollet et al. (1996), or over Albertsen et al. (US 6,114,124 issued 2000) or over Ikawa et al. (1988), and Buck et al. (1999) and Stratagene (1988 catalog).

Claim 7 has been cancelled.

Claim 9 has been amended to recite that the primers are part of a kit which includes instructions as to the use of the primers in the novel process of claim 1.

Claims 11 is a method claim claiming the use of the kit in the novel method of claim 1.

Although the multiple references cited by the examiner include analogues or sequences which include a portion of the claimed sequences or of which the claimed sequences are a portion none of the references considered individually or in combination disclose or suggest their use in the novel process of claim 1 nor do they include directions as how to perform the novel process of claim 1.

Applicant believes the new limitation in the amended claims defeats any *prima facie* case of obviousness that may have existed and requests favorable reconsideration of these grounds for rejection.

Claims 1, 4-6, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et a., Davies et al, Kmiec et al.(W0200173002 published 2001), Shuber et al. (W0200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (1996), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999).

This rejection is based on the examiner's extensive search of the prior art and citation of an extensive combination of references each containing a smaller or larger fragment of the teaching of applicant's claims. Applicant acknowledges that this is the usual procedure for establishing a *prima facie* case but believes that the examiner has gone too far in piecing together all these references.

Applicant traverses this ground for rejection on several bases:

1. the sheer volume of references uncovered by the examiner demonstrates that this is crowded art and the many workers skilled in the art are working in the field.

2. the references cited by the examiner are as much as 2 decades old (Stratagene) and most are at least 10 years old.

3. the volume of work going on in the field, the long period in which work has been ongoing and disclosure of bits and pieces would logically demand that the superior results obtained by applicant in his claimed method would have uncovered at least

a decade ago if it were obvious to combine those bits and pieces.

4. the number of references showing bits and pieces is merely an invitation to experiment among the thousands or combinations and permutations possible in combining the teacgings of the various references.

5. the most important factor demonstrating the unobviousness of applicant method are the superior and unexpected results applicant has obtained.

The subject matter is a method for the non-invasive early detection of cancer colon (colorectal carcinoma) or intestinal cancer precursor cells using analysis of genes which are known and which react on a defined signal pathway. Is it already known that so called marker genes exist which can mutate and the that the signaling pathway is reprogrammed during the genesis of colon cancer resulting in the cells reacting with uncontrolled overgrowth.

The two important signaling pathways (in connection with colon cancer) which are known are the Wnt pathway and the MAPK pathway. Mutations in Wnt genes or Wnt pathway components lead to specific developmental defects and cancer is caused by abnormal Wnt signaling. The APC- and the l3-catenin-gene are two genes known to react on the Wnt pathway.

The MAPK pathway is very complex and includes many protein components. The series of kinases from RAS-RAF to MEK to MAPK is an example of a protein kinase cascade. The K-Ras and the B-Raf- gene are two known genes of the MAPK pathway in connection with colon cancer. By mutation of one of these genes

the MAPK signaling pathway is permanently disordered.

The idea and subject matter of the present invention is now the combination of the analysis of four marker genes of colon cancer wherein only two genes of the one signaling pathway are combined with two genes known to react of the another signaling pathway. That means the present invention shows a method using a combination of gene markers having defined primer pairs for the four genes APC-and the R-catenin as well as K-Ras and BRaf which cover the Wnt and Ras-Raf-MEK-MAPK signalling pathways.

The aim was the detection of colon cancer 1) at a very early stage 2) by stool DNA analysis. That can be done by the claimed method using the well defined primer panel which identifies AFC, K-Ras, B-Raf and 13-Catenin (also known as CTNNB1) mutations. The use of the defined primer combination as claimed in claim 1 was not present in nor obvious from the prior art.

In this connection applicant refers to the enclosed publication of the inventors in Cancer Epidemiology 33 (2009) 123-129. There is shown that about 80% of early stage colorectal carcinomas (CRC) - UICC-stage I - are detectable for the first time by use of the new primer panel of the present invention (see page 124, left column, [24]).

The sensitivity of CRC detection (%) can be seen from Table 4 on page 126. It clearly demonstrates that the difference with regard to stage II carcinomas and stage IV carcinomas the combination with the well known MSI analysis (see page 124-125, item 2.5. and Table 4) did not enhance the

percentage of tumors being positive in the case of stage I tumors.

This surprising and immensely significant finding demonstrates that for the first time Stage I carcinomas can be detected with the same assurance level as later stage carcinomas.

The claimed method using the defined primers of the four marker genes analyzed represent early and initiating mutations in CRC development with high accuracy. This was not obvious and very surprising and coupled with the other considerations set forth above is believed to obviate any prima facie case of obviousness that may have existed.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (W0200173002 published 2001), Shuber et al. (W0200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (W02002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Gerry et al. (1999).

As a *prima facie* case of obviousness has not been made out as against the independent claim, claim 1, dependent claim 2 is also not obvious.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (W0200173002 published 2001), Shuber et al. (W0200118252 published 2001), Ferrie et al. (GB2327497

published 1999), Coste et al. (1998), Nollet et al. (W02002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Shuber et al. (W0199858081 published 1998).

As a *prima facie* case of obviousness has not been made out as against the independent claim, claim 1, dependent claim 3 is also not obvious.

Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002), Kmiec et al. (W0200173002 published 2001), Shuber et al. (W0200118252 published 2001), Ferrie et al. (GB2327497 published 1999), Coste et al. (1998), Nollet et al. (W02002058534 published 1 August 2002), Albertsen et al. (United States Patent 6,114,124 issued 2000), Ikawa et al. (1988), and Buck et al. (1999) as applied to claim 1 above, and further in view of Baba et al. (1996).

As a *prima facie* case of obviousness has not been made out as against the independent claim, claim 1, dependent claims 12 and 13 are also not obvious.

Conclusion

Favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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